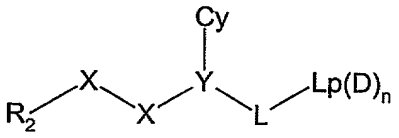
Claims

1. A serine protease inhibitor compound of formula (I)



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not unsubstituted aminoalkyl;

Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups R_{3a} or $R_{3i}X_i$;

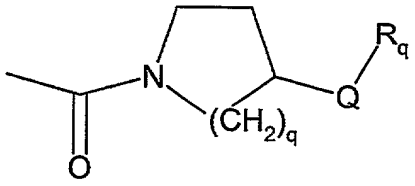
each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkylimidazolyl, thiazolyl, alkylthiazolyl, alkyloxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group), or $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy;

X_i is a bond, O, NH or CH_2;

R_{3i} is phenyl, pyridyl or pyrimidinyl optionally substituted by R_{3a}; and

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a},

and $-L-Lp(D)_n$ is of the formula:



wherein:

q is 1 or 2;

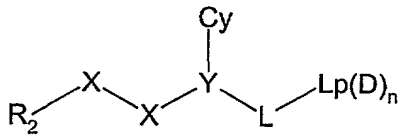
Q is -O- or -NH-;

and R_q is R_c which is pyridyl, pyrimidin-4-yl, pyridazin-3-yl, pyridazin-4-yl or phenyl (which phenyl or pyridyl group may bear a fluoro, chloro, alkyl, $CONH_2$, SO_2NH_2, dialkylaminosulphonyl, methoxy, methylthio, alkylsulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, alkoxycarbonyl, acetylamino, cyano, ethoxy, nitro, hydroxy,

alkylsulphonylamino, triazolyl or tetrazolyl substituent);

or a physiologically-tolerable salt thereof.

2. A serine protease inhibitor compound of formula (I)



(I)

wherein:

R_2 is a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of X-X) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, $MeSO_2$- or R_1, or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R_{1j}, and optionally substituted in the position alpha to the X-X group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio with the proviso that R_2 cannot be aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO, CR_{1a}, $C(R_{1a})_2$ or NR_{1a} group, at least one X being C, CO, CR_{1a} or $C(R_{1a})_2$;

each R_{1a} independently represents hydrogen, hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

R_1 is as defined for R_{1a}, provided that R_1 is not

unsubstituted aminoalkyl;

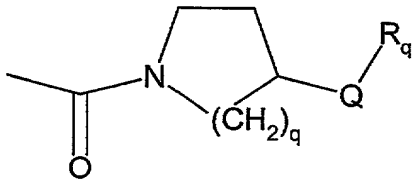
Y (the α-atom) is a nitrogen atom or a CR_{1b} group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R_{3a} or phenyl optionally substituted by R_{3a};

each R_{3a} independently is R_{1c}, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl; and

R_{1b}, R_{1c} and R_{1j} are as defined for R_{1a},

and -L-Lp(D)$_n$ is of the formula:



wherein:

q is 1 or 2;

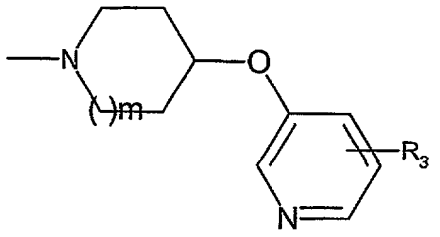
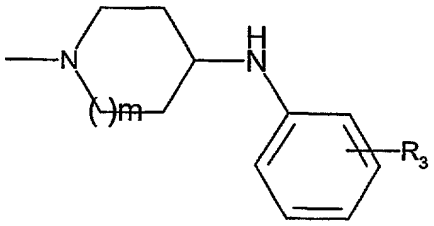
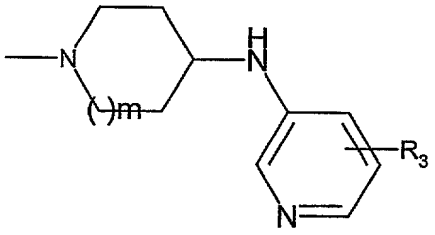
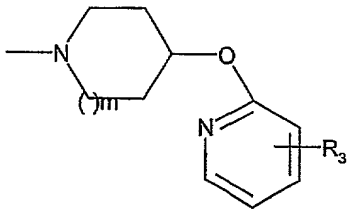
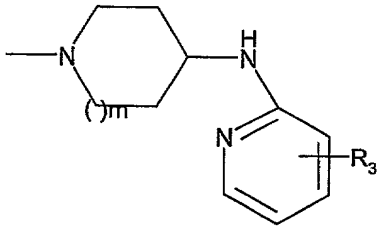
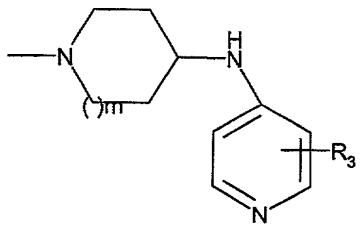
Q is -O- or -NH-;

and R_q is R_c which is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, $CONH_2$, SO_2NH_2, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent);

or a physiologically-tolerable salt thereof.

3. A compound according to either claim 1 or claim 2 wherein q is 2.

4. A compound according to any of claims 1 to 3 wherein -Lp(D)n is selected from the following formulae:

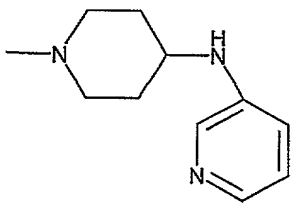
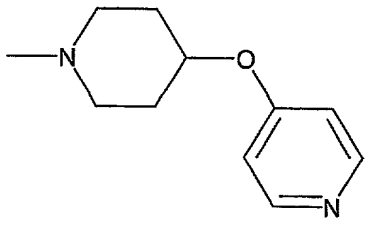







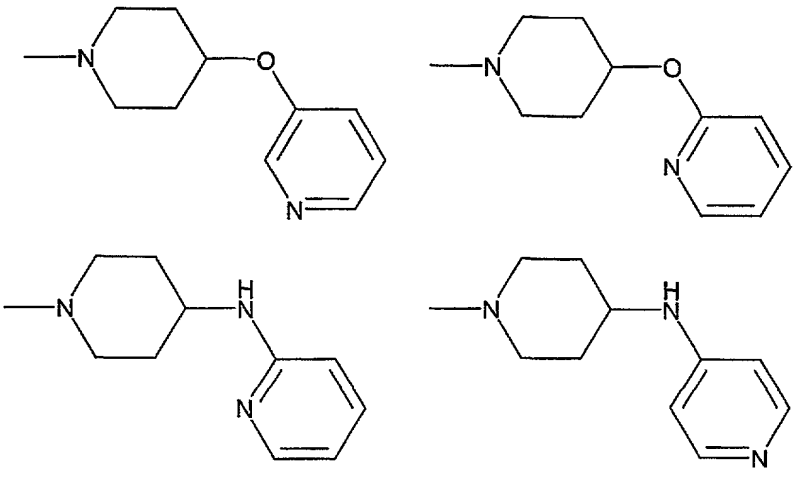
wherein:

m represents 0 or 1; and

when R_3 is present as a substituent on an aromatic ring, it is selected from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxycarbonyl, acetylamino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

5. A compound according to any of claims 1 to 3 wherein - Lp(D)n is selected from the following formulae:



6. A compound according to any one of claims 1 to 5 wherein Q is -NH-.

7. A compound according to any of claims 1 to 3 wherein Rc is pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimid-4-yl or phenyl.

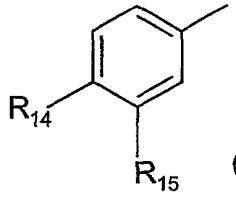
8. A compound according to any of claims 1 to 3 wherein Rc is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methylsulfonylphenyl, 2-methylthiophenyl, pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

9. A compound according to any one of claims 1 to 8 wherein R_2 is phenyl, thien-2-yl, naphthyl, indol-2-yl, indol-6-yl, benzo[b]furan-5-yl, benzo[b]thiophen-2-yl or benzimidazol-2-yl (each of which is optionally substituted as defined in claim 1).

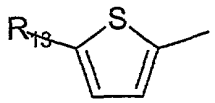
10. A compound according to any one of claims 1 to 9 wherein optional substituents for R_2 are selected from: fluoro, chloro, bromo, iodo, nitro, thiol, difluoromethoxy, trifluoromethoxy, hydrazido, methylhydrazido, amino, cyano, trifluoromethyl, methylthio, vinyl, ethynyl, acetylamino,

carboxy, acetoxy, hydroxy, methyl, ethyl, amido ($CONH_2$), aminomethyl, methoxy and ethoxy.

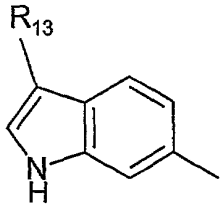
11. A compound according to any one of claims 1 to 10 wherein R_2 is selected from one of the formula (A') to (H'):



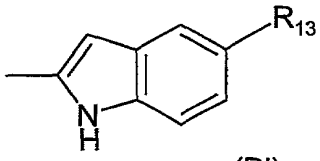
(A')



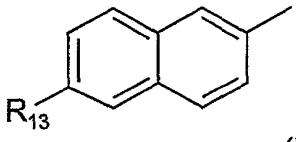
(B')



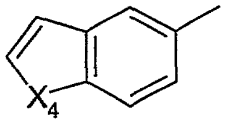
(C')



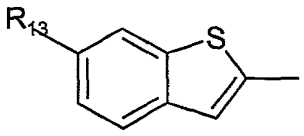
(D')



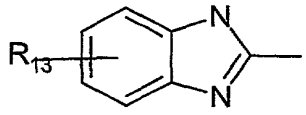
(E')



(F')



(G')



(H')

wherein X_4 is O or S, R_{13} is selected from hydrogen, chloro or methyl and R_{14} is selected from hydrogen, methyl, ethyl, fluoro, chloro, and methoxy and R_{15} is selected from hydrogen, methyl, fluoro, chloro and amino.

12. A compound according to claim 11, wherein R_2 is 4-methoxyphenyl, 5-chloroindol-2-yl, 3-chloroindol-6-yl, indol-6-yl or 3-methylindol-6-yl.

13. A compound according to any one of claims 1 to 12 wherein -X-X- is -CONH-.

14. A compound according to any one of claims 1 to 13 wherein Y is CH.

15. A compound according to any one of claims 1 to 14 wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, imidazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, pyrimidinyl, pyridazinyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl or cycloalkyl group, or a phenyl group substituted by $R_{3i}X_i$ in which X_i is a bond, O, NH or CH_2 and R_{3i} is phenyl or pyridyl optionally substituted by R_{3a}.

16. A compound according to any one of claims 1 to 14, wherein Cy is an optionally R_{3a} substituted: phenyl, pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

17. A compound according to any one of claims 1 to 16 wherein R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy, haloalkyl, a

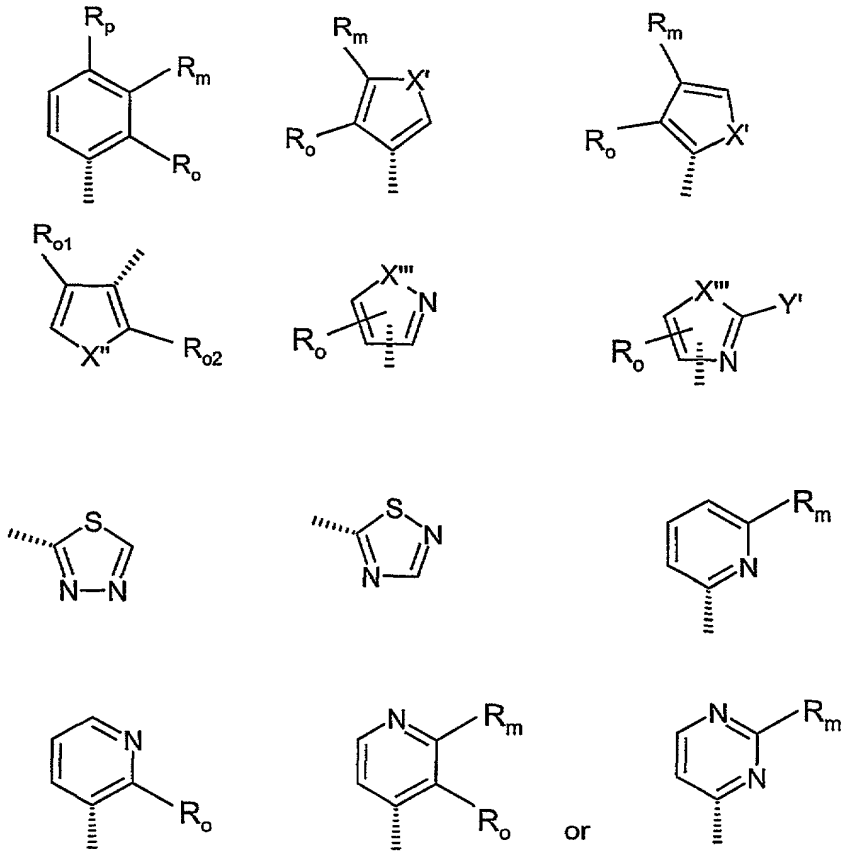
group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S; and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group) and $-OCH_2O-$ which is bonded to two adjacent ring atoms in Cy.

18. A compound according to any one of claims 1 to 16 wherein R_{3a} is selected from hydrogen, hydroxyl, alkoxy, alkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), aminoalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), hydroxyalkyl (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, alkylamino (optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl), amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl.

19. A compound according to any one of claims 1 to 16 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, bromo, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl, bromo, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-1-ylcarbonyl and $-OCH_2O-$ (which is bonded to two adjacent ring atoms in Cy).

20. A compound according to any one of claims 1 to 16 wherein R_{3a} is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, $CONH_2$, CH_2CONH_2, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, methylsulphonylamido, ethylsulphonylamido, methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

21. A compound according to any one of claims 1 to 16 wherein Cy is selected from:



wherein:
X' is selected from O, S and NMe;
X'' is selected from O and S;
X'" is selected from O, S, NH and NMe;
Y' is selected from hydrogen, amino and methyl;
R_o is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl and methylsulphonyl;
R_m is selected from hydrogen, methyl, fluoro, chloro, trifluoromethyl, methoxy, methylthio, methylsulphinyl, methylsulphonyl, carboxy, methoxycarbonyl and a group of the formula $-C(X^3)N(R^{11})R^{12}$ (wherein X^3 is O or S, and R^{11} and R^{12} are independently selected from hydrogen, methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidin-1-yl, piperidin-1-yl or morpholino group);
R_p is selected from hydrogen and fluoro; or
R_o and R_m or R_m and R_p form an -OCH2O- group; or
R_o and R_m together with the ring to which they are attached form a 5 or 6 membered aryl or heteroaryl ring (wherein the heteroary ring contains 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur); and
one of R_{o1} and R_{o2} is hydrogen and the other is R_o.

22. A compound according to any one of claims 1 to 16 wherein Cy is selected from phenyl, 2-chlorophenyl, 2-methoxyphenyl, 4-carbamoylphenyl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, thien-2-yl, thien-3-yl, furan-2-yl, furan-3-yl, imidazol-2-yl, thiazol-2-yl, thiazol-4-yl, 2-amino-thiazol-4-yl, thiazol-5-yl, naph-1-thyl, isoquinolin-5-yl, isoquinolin-8-yl, quinolin-4-yl, quinolin-5-yl and quinolin-8-yl.

23. A compound as claimed in Claim 1, which is selected from 1-(indol-6-carbonyl-D-phenylglycinyl)-4-(4-pyridoxy)-

piperidine; 1-[indole-6-carbonyl-D,L-(2-chlorophenyl)glycinyl]-4-(pyridin-4-yloxy)piperidine, and physiologically-tolerable salts thereof.

24. A compound as claimed in any one of Claims 1 to 23, in which the alpha atom in Y is carbon and has the conformation that would result from construction from a D-α-aminoacid NH_2-CR_{1b}(Cy)-COOH where the NH_2 represents part of X-X.

25. A pharmaceutical composition, which comprises a compound as claimed in any one of Claims 1 to 24 together with at least one pharmaceutically acceptable carrier or excipient.

26. A compound as claimed in any one of Claims 1 to 24 for use in therapy.

27. Use of a serine protease inhibitor according to any one of Claims 1 to 24 for the manufacture of a medicament for the treatment of a thrombotic disorder.

28. A pharmaceutical composition, which comprises a compound as claimed in any one of Claims 1 to 24 together with at least one pharmaceutically acceptable carrier or excipient for use in the treatment of a thrombotic disorder.

29. A method of treatment of the human or non-human animal body to combat a thrombotic disorder, said method comprising administering to said body an effective amount of a compound according to Claim 1.

30. A compound of formula I as claimed in Claim 1 and named in any one of the Examples herein, or a physiologially acceptable salt thereof.